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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JOHN M. POLO, THOMAS W. DUBENSKY, JR.,
BARBARA A. BELLI, SILVIA PERRI, and TIMOTHY C. FONG

Appeal 2007-4290
Application 09/546,201
Technology Center 1600

Decided: February 29, 2008

Before TONI R. SCHEINER, LORA M. GREEN, and
RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal from the final rejection of claims 26, 28-31, and 33-44. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF CASE

This appeal relates to the field of genetic engineering. The claims are directed to an "expression cassette," such as a plasmid, for producing double

stranded RNA ("dsRNA") and an antigen from a pathogenic agent. The Specification describes the expression cassette for "increasing, enhancing, or stimulating an immune response" (Spec. 3: 14-21) which in turn is useful for prophylactic or therapeutic vaccination (*id.*, at 3: 8-12).

Claims 26, 28-31, and 33-44 are pending and appealed (App. Br. 2). There is one rejection at issue in this appeal: Claims 26, 28-31, and 33-44 as obvious under 35 U.S.C. § 103(a) over Dubensky (U.S. Pat. No. 6,015,686, Jan. 18, 2000), Cella (*J. Exp. Med.*, 189: 821-829, 1999), Chada (U.S. Pat. No. 5,736,388, Apr. 7, 1998), and Gillespie (WO 90/14090, Nov. 29, 1990) (Ans. 3).

Appellants have not provided separate reasons for the patentability of any claims. Consequently, the claims stand or fall together with respect to the obviousness rejection. *See* 37 C.F.R. § 41.37(c)(1)(vii). We choose claim 26, which reads as follows, as representative for deciding the obviousness rejection:

> 26. An expression cassette comprising
> a promoter operably linked to a nucleic acid molecule which, when transcribed in vivo, forms double stranded RNA via self-complementing sequences within the RNA, wherein the double stranded RNA induces the production of interferon, and
> an RNA polymerase II promoter operably linked to a nucleic acid molecule that encodes an antigen from a pathogenic agent.

ISSUE ON APPEAL

The Examiner contends that the claimed expression cassette would have been obvious to persons of ordinary skill in the art in view of Dubensky, Cella, Chada, and Gillespie. Appellants contend that there would

have been no motivation to have combined the cited prior art to arrive at the claimed invention.

The issue in this appeal is whether the Examiner erred in the determination that the claimed expression cassette is obvious over Dubensky, Cella, Chada, and Gillespie.

ANALYSIS

The "Examiner bears the initial burden, on review of the prior art . . , of presenting a prima facie case of unpatentability." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). In making an obviousness determination, the Examiner must first identity the scope and contents of the prior art and then ascertain the differences between the prior art and the claimed invention. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Thus, we first turn to the prior art. The following numbered findings of fact ("FF") summarize the prior art relied upon by the Examiner in setting forth the basis of the rejection (Answer 3-7):

Scope and contents of the prior art

Dubensky Patent

1. Dubensky describes an alphavirus vector system containing a 5' promoter for expressing heterologous sequences (Dubensky, at col. 2, l. 53 to col. 3, l. 50).

2. The system can be used for various purposes, including as a vaccine "for stimulating a specific immune response and inhibiting viral spread" (*id.*, at col. 37, ll. 17-63).

3. The 5' promoter can be an RNA polymerase II promoter, such as CMV, SV40, or MoMLV LTR (*id.*, at col. 12, ll. 53-62; at col. 55, ll. 15-36; Ans. 4).

4. The promoter can be used to express viral antigens, including HIV, HSV, HBV, HCV, HPV, and FIV (*id.*, at col. 4, ll. 36-46; Ans. 4).

5. The vector can also encode bacterial, parasitic, and fungal proteins (*id.*, at col. 23, ll. 30-36; Ans. 4).

6. "A wide variety of heterologous sequences may be included in the vector construct, including . . . antigens which stimulate an immune response . . . , as well as antisense sequences" (*id.*, at col. 20, ll. 15-25; *see* Ans. 5).

7. Antisense RNA can be utilized to induce the formation of interferon in cells harboring the vector system; "high levels of specific antisense are believed to induce the increased expression of interferons . . . due to the formation of large quantities of double-stranded RNA" with naturally occurring RNA, such as actin, myosin, and histone (*id.*, at col. 23, ll. 1-13; *see* Ans. 5).

Gillespie

8. Gillespie describes the synthesis of double stranded RNA using a plasmid vector (Gillespie, at 5, l. 2 to 6. 25; Ans. 5).

9. The double stranded RNA is biologically active, but non-toxic to cells (*id.*, at 2, ll. 3-23), and can be used to induce interferon (*id.*, at 1, ll. 12-13; at 10, cl. 10; Ans. 5).

10. A plasmid vector, pGEM 4, is described which contains a promoter and nucleic acid that is used to produce single-stranded and complementary

RNAs that are annealed to each other, forming the double-stranded RNA (*id.*, at 5, ll. 2-21; Fig. 2).

Cella

11. According to Cella, the "initiation of an immune response is critically dependent on the activation of dendritic cells (DCs)" (Cella, at 821 ("Summary")).

12. Cella shows that human DCs are activated by viral infection and by double-stranded RNA, "a classical inducer of type I interferon . . . which plays a critical role in antiviral responses" (*id.*, at 826, col. 2; Ans. 6).

13. Cella teaches that dsRNA induces two distinct responses in DC which are necessary to optimize loading of viral antigens on MHC molecules for antigen presentation (*id.*, at 826, cols. 1-2; Ans. 6).

Chada Patent

14. Chada describes a eukaryotic layered vector initiation system which utilizes the same viral vectors and promoters as those in Dubensky's system (*see* Chada, at col. 14, ll. 52-56; at col. 16, l. 48 to col. 17, l. 21; Ans. 7).

15. Chada states that one promoter within the same multivalent vector having more than one gene of interest may be inadequate to ensure an adequate levels of expression of all genes present in the vector, and thus teaches using two or more promoters to solve this problem (*id.*, at col. 26, ll. 4-17; Ans. 7).

Differences between the claimed invention and the prior art

Once the scope and contents of the prior art has been determined, the next step is to identify the differences between the prior art and the claimed

invention. *Graham*, 383 U.S. at 17. The following numbered findings of fact are pertinent to this issue:

16. Claim 26 is directed to an expression cassette that comprises two elements:

17. (1) a promoter which is linked to and drives the transcription ("operably linked to") of a nucleic acid which forms double stranded RNA in vivo via complementary sequences ("self-complementing") with the RNA; and

18. (2) an RNA polymerase II promoter which is linked to and drives the transcription ("operably linked to") of a nucleic acid that encodes an antigen of a pathogen.

19. Thus, the expression cassette – which can be present in a vector, such as a plasmid[1] – contains two regions which, when expressed, produce (1) double stranded RNA; and (2) an antigen of a pathogen, respectively.

20. The RNA polymerase II promoter can be CMV, SV40, MoMLV LTR, and RSV LTR (Spec. 5: 4-12; instant claim 33).

21. The antigen pathogen can be from a virus (e.g., HIV, HSV, HBV, HCV, HPV, and FIV), bacteria, parasites, and fungus (Spec. 5: 12-16; instant claims 29 and 30).

22. Dubensky describes a vector system for expression of heterologous sequences, such as viral, bacterial, parasitic, and fungal antigens (FF 1, 4, 5) – the same type which is claimed (FF 18, 21).

23. Dubensky also discloses RNA polymerase II promoters to drive expression of the pathogen antigen (FF 3) – which is also the same class of promoters recited in claim 26 (FF 18, 20).

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[1] *See* claims 34 and 35.

24. In sum, Dubensky describes an RNA polymerase II promoter linked to and driving the expression of a sequence of a pathogen antigen (FF 22, 23), meeting the limitation of claim 26 of (2) "an RNA polymerase II promoter operably linked to a nucleic acid molecule that encodes an antigen from a pathogenic agent" (FF 16, 18).

25. Dubensky does not teach (1) "a promoter operably linked to a nucleic acid molecule which, when transcribed in vivo, . . . via self-complementing sequences within the RNA, wherein the double stranded RNA induces the production of interferon" as recited in claim 26 (FF 16, 17).

26. However, Dubensky describes the expression of heterologous sequences in its vector, in addition to the pathogen sequence (FF 6), including an antisense RNA which forms double stranded RNA that "induce[s] interferons" (FF 7; Dubensky, at col. 23, ll. 1-13; Ans. 5).

27. Thus, while the Dubensky patent does not describe a vector containing both copies of the complementary RNA which anneal, in vivo, to form double stranded RNA (FF 16, 17), the patent does teach production of double stranded RNA in vivo which is facilitated by a promoter as in element (1) of claim 26 and in combination with pathogen expression as in element (2) of the claim (FF 17-19).

28. With respect to the limitation that "a nucleic acid molecule which, when transcribed in vivo, forms double stranded RNA via self-complementing sequences" (FF 17, 25), Gillespie describes a plasmid vector containing an RNA promoter that is used to transcribe complementary RNAs that anneal to form double stranded RNA (FF 8-10).

29. Gillespie does not describe the annealing step to form double stranded RNA as occurring in vivo, and thus does not meet the limitation in claim 26 that the promoter "when transcribed in vivo, forms double stranded RNA" (FF 17, 25).

Level of skill in the art

When making an obviousness determination, the scope of the prior art and level of ordinary skill must be considered. *Graham*, 383 U.S. at 17. The following findings summarize the level of ordinary skill in the art:

30. Persons of ordinary skill in the art were familiar with making vector constructs, including modifying vectors to contain more than one heterologous sequence, each with its own promoter (FF 14, 15; Ans. 7) and choosing particular heterologous sequences to include within it (FF 4-6).

31. Persons of ordinary skill in the art would have known that forming a double stranded RNA molecule requires substantial complementarity between the two RNA single strands.

Motivation to combine the prior art

Once the differences between the prior art and the claimed invention have been ascertained, the next step is to identify motivation or a reason why persons of ordinary skill in the art would have been prompted to combine the prior art to have made the claimed invention. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). The following findings are relevant to this determination:

32. Cello's teaching that double stranded RNA and viral antigens are critical for an antiviral response and necessary to optimize loading of viral antigens for antigen presentation (FF 11-13) would have motivated persons of

ordinary skill in the art to co-administer double stranded RNA and viral antigens in order to stimulate the immune response (Ans. 6).

33. Dubensky describes a vector system for expressing viral antigens which can be used to stimulate an immune response to the expressed antigen (FF 1, 2, 4; Dubensky, at col. 37, ll. 17-63; at col. 4, ll. 36-46; Ans. 4).

34. Dubensky states that its vector can further comprise heterologous sequences to stimulate the immune response, including antisense RNA to make double stranded RNA in vivo (FF 6, 7; Dubensky, at col. 20, ll. 15-25; at col. 23, ll. 1-13; Ans. 5).

35. Thus, Dubensky teaches a vector which could be used to co-administer double stranded RNA and viral antigens as suggested by Cello as being critical for an antiviral response (FF 32).

36. Persons of ordinary skill in the art would have been motivated to substitute the antisense in Dubensky's vector with "a nucleic acid molecule which . . . forms double stranded RNA" (claim 26) as taught by Gillespie (FF 8-10; Gillespie, at 5, l. 2 to 6, l. 25; Ans. 5) for its expected benefit in inducing interferons, without toxicity (FF 9; Gillespie, at 2, ll. 2-23; at 1, ll. 12-13; at 10, cl. 10).

37. Persons of ordinary skill in the art would also have been motivated to have utilized Gillespie's nucleic acid molecule for producing double stranded RNA in Dubensky's vector system for the molecule's known advantage in inducing interferon (Ans. 5).

38. There would have been a reasonable expectation that Gillespie's nucleic acid molecule construct would produce interferon in vivo, when expressed by Dubensky's vector, because Dubensky's teaches that double stranded

RNA, capable of inducing interferons, forms in cells harboring its vector system (FF 7).

39. The modification of Dubensky's vector by replacing the antisense with Gillespie's nucleic acid molecule would have been with the skill of the ordinary artisan who was familiar with making vector constructs, including modifying vectors to contain more than one heterologous sequence, each with its own promoter (FF 30; Ans. 7).

Because we conclude that there is sufficient evidence to establish prima facie obviousness of the claimed subject matter, including adequate reasons to have combined Dubensky with Gillespie's teaching (FF 32-39), we turn to Appellants' rebuttal arguments and evidence. *See Hyatt v. Dudas*, 492 F.3d 1365, 1369-70 (Fed. Cir. 2007).

Appellants argue that there was no motivation to have combined the cited prior art (App. Br. 10). They contend that "none of the references teach or suggest that antisense RNA and dsRNA formed in vivo via self-complementation are somehow interchangeable" (App. Br. 11; *see also* Reply Br. 5-6). They assert that Gillespie does not teach double stranded RNA is formed in vivo, but rather "makes it plain" that it should be produced in vitro prior to administration to a subject (App. Br. 7). The

> evidence of record clearly indicates that the ability to induce interferon production is <u>not</u> a sufficient grounds to assert that an antisense-mRNA molecule is necessarily an "obvious alternative" to dsRNA formed in vivo by self-complementation. Not only is there nothing in Dubensky, Chada or Cella regarding dsRNA formed via self-complementation, Dubensky explicitly teaches that increased expression of interferons results from "large quantities" of double-stranded antisense-mRNA molecules and, indeed, indicates that in order to have

> sufficiently large quantities of the antisense-mRNA hybrids, antisense RNA that is specific for common mRNA transcripts (actin, myosin, histone) is preferred.

(App. Br. 12.)

We are not persuaded by this argument that the Examiner erred. It is true that Gillespie does not teach its vector as useful for forming double stranded RNA in vivo as required by claim 26. However, Dubensky clearly teaches that double stranded RNA can be formed in vivo between an antisense and a naturally occurring RNA, such as actin RNA (FF 7; Dubensky, at col. 23, ll. 1-13; *see* Ans. 5). Thus, persons of skill in the art would have reasonably expected that Gillespie's nucleic acid molecule construct would produce double stranded RNA in vivo, when expressed by Dubensky's vector (FF 38). The only difference is that, in Dubensky's system, one single stranded RNA is provided as an expression product of the vector and the other single stranded RNA is provided by the cell. In contrast, Gillespie's vector provides both copies of the single stranded RNA. Thus, we agree with Examiner that the two approaches are interchangeable in that they both accomplish the same purpose: production of double stranded RNA.

A suggestion, teaching, or motivation to combine the relevant prior art teachings does not have to be found explicitly in the prior art. *In re Kahn*, 441 F. 3d 977, 988 (Fed. Cir. 2006). *See also Dystar Textilfarben Gmbh & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1367 (Fed. Cir. 2006) (The "suggestion test is in actuality quite flexible and not only permits, but requires, consideration of common knowledge and common sense."). Thus, it is not necessary that prior art explicitly suggest that

Dubensky's antisense could be replaced with Gillespie's. In this case, persons of ordinary skill in the art would have recognized that Gillespie's nucleic acid would be equally as capable as Dubensky's antisense strategy of making double stranded RNA with interferon-inducing activity. Thus, the prior art teaching of the benefit of co-expression of double stranded RNA with viral antigens to simulate the immune response (FF 7, 12, 13, 32, 34) would have led persons of ordinary skill to have utilized Gillespie's system for its known function (FF 36). When "a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious." *KSR*, 127 S. Ct. at 1740.

Appellants state that "Dubensky and/or Chada do not teach that dsRNA will induce interferon production. Rather these references teach that inducing interferon production requires the use of specific antisense molecules" (Reply Br. 4).

We do not agree. Dubensky explicitly states the reason for producing antisense RNA with its vector is to facilitate the formation of double stranded RNA (FF 7; Dubensky, at col. 23, ll. 1-13). Dubensky's reference to "specific antisense" would be understood by the ordinary skilled artisan to mean an antisense having a specific sequence which is complementary to, e.g., actin, myosin, or histone RNA (*id.*) because forming a double stranded molecule requires substantial complementarity between the single strands (FF 31). Thus, Appellants' statement that Dubensky does not "teach or suggest dsRNA formed via self-complementation" (Reply Br. 5) is an oversimplification. In fact, Dubensky teaches double stranded RNA formed

by complementarity between the antisense and a naturally occurring RNA. This is the same mechanism utilized by Gillespie, but Gillespie's vector supplies copies of both complementary RNAs, rather than only one as in Dubensky.

Persons of ordinary skill in the art were familiar with making vector constructs, including choosing heterologous sequence to include within it (FF 31). Thus, the type of choice upon which the rejection is based – using Gillespie's nucleic acid molecule in place of Dubensky's antisense – would have been the same kind of activity that the skilled artisan ordinarily engages in when constructing vectors. The obviousness analysis "can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 127 S. Ct. at 1741.

It is also stated by Appellants that "one of ordinary skill in the art would read Dubensky and Chada as teaching away from using self-complementing dsRNA instead of antisense because self-complementing dsRNA is not specific and the quantities needed are unknown" (Reply Br. 5-6). We do not find this argument persuasive. As explained above, Dubensky's mention of "specific antisense" refers to it being specifically complementary to an RNA in the cell in order to form double stranded RNA. Self-complementary RNA contains two copies of RNA – each of which are specific for each other. Thus, Appellants have not properly distinguished the claimed invention from the prior art.

Appellants also argue that Gillespie "does not actually demonstrate that such [dsRNA] sequences actually induce interferon production (App. Br. 12). We are not convinced by this argument. Gillespie clearly teaches

that its dsRNA would be capable of inducing interferon. It is Appellants' burden to show that Gillespie is not enabling for interferon induction, and they have not provided any evidence to establish that.

For the foregoing reasons, we affirm the rejection of claim 26. Claims 28-31 and 33-44 fall with claim 26 because separate reasons for their patentability were not provided.

TIME PERIOD

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED.

Ssc:

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